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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/564,932
Filing Date: January 13, 2006
Appellant(s): THEOBALD ET AL.

Cathy R.Moora
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on 10/15/2010 appealing from the Office action mailed 06/18/2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendments after final rejection have been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

WO 03/015779 equivalent to US publication 2004/0247656	Beier et al. et al.	12-2004
US 5939094	Durif et al.	08-1999
US 4769028	Hoffmann	09-1988
US 5,112,842	Zierenberg et al.	05-1992
WO 96/39136	Patel	12-1996
US 5,238,944	Wick et al.	08-1993

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims :

Claim Rejections - 35 USC § 112

(New matter rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 and dependent claims 2-3, 6-12, 14-17 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 recites "the polymer layer is disposed **directly** on the backing layer" in the first line of the claim.

For the amendment to instant claim 1 which included the term "directly" applicants state that the support can be found in their application as filed on page 12, lines 15-25. However, it is noted that the lines cited by the applicant recite as follows:

> Example 2
> A TTS consisting of backing layer and two active ingredient-containing layers is produced. The first active ingredient-containing layer (reservoir layer) consists of 40 % by weight of pramipexol (base) and 60 % by weight of Durotak 2287 and has a basis weight of 100 g/m^2. The second active ingredient-containing layer (pressure-sensitive adhesive layer) consists of 3 % by weight of pramipexol (base) and 97 % by weight of Durotak 2287 and has a basis weight of 30 g/m^2. TTS samples for the in vitro investigations are cut out of

The above recitation is just stating that a TTS consisting of a backing layer and two active ingredient-containing layers is produced. Nowhere in the recitation does it state that "**the polymer layer is disposed directly on the backing layer".** Other

sections of the instant disclosure also fail to lend support to this limitation. As such introduction of the term "directly" in instant claim 1 constitute new matter.

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that the Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975. Accordingly, claims 6 and 7 are properly rejected under 35 U.S.C. 112 for new matter addition in the claims. Accordingly, claims 1 and dependent claims 2-3, 6-12, 14-17 and 19-20 are properly rejected under 35 U.S.C. 112 for new matter addition in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Rejection of claims 1-3, 6-12 14-16 and 17-20 under 35 U.S.C. 103(a) as being unpatentable over Beier et al.(WO 03/015779 as translated by US 2004/0247656,) in view of Durif et al. et al (US 5939094) and Hoffman et al (US 4769028) further in view of Zierenberg et al. et al, (US 5112842, already of record) and Patel (WO 96/39136) is maintained for reasons of record restated below.

Amendment to instant claim 1 adds the new limitation that the polymer layer is disposed directly on the backing layer. In the following rejection, Hoffmann et al.teaches a transdermal patch comprising a protective impermeable backing layer followed by a reservoir layer (col.2, lines 4-21 and 47-68, col. 3, lines 4-6, claim1) where in the reservoir layer comprises a polymer matrix with a carrier agent or a therapeutic agent (col.3, lines 47-66). Absence of evidence to the contrary, the reservoir polymer layer of Hoffman's transdermal patch is disposed directly on the backing layer.

New claims 19 and 20 essentially recite the limitations which have already been addressed in the previously submitted claims 1-3, 6-12 and 14-18.

For e.g.: New claim 19 recites as follows:

19. (New) The transdermal therapeutic system as claimed in Claim 1, wherein the first and second active ingredient-containing polymer layers comprise pressure-sensitive adhesive polymer consisting of carboxyl group-free polyacrylates that do not comprise water or an aqueous dispersion, and the transdermal therapeutic system releases the active ingredient pramipexol with a flux rate greater than 5 µg/cm2 hr over the period between 24 hours after administration to 72 hours after administration in the absence of a penetration-promoter, and said system has no additional pressure sensitive adhesive top plaster for fixing to the skin.

20. (New) The transdermal therapeutic system as claimed in claim 19, wherein the first and second active ingredient-containing polymer layers consist of pramipexol and carboxyl group free polyacrylates pressure-sensitive adhesive.

With reference to New claim 19, previously presented claim 16, recited pressure sensitive adhesive polymer which do not comprise water or aqueous dispersion, currently amended claim 1 and previously presented claim 12 had the limitation of the release rate of the active ingredient pramipexol being at a flux rate of greater than 5 µg/cm2 over a period between 24 hours after administration to 72 hours after administration and currently amended claim 18, had the limitation that the system has no additional pressure sensitive adhesive top plaster for fixing to the skin.

With reference to new claim 20 limitations, these limitations are addressed in the following rejection as the limitations were recited in the previously presented claims 1 and 12.

With regards to the limitations in the new claim 19 "in the absence of a penetration-promoter, Beier et al.teaches a transdermal therapeutic system for the administration of pramipexol comprising an (i) an active ingredient-impermeable cover layer (ii) a plurality of active ingredient containing matrix layer (iii) a peel-off protective layer (claim 1) which does not include a penetration enhancer. In addition Beier et

al.teaches that the matrix patch of his invention to consists of an impermeable cover layer, one or more self-adhesive matrix layer and where applicable a permeation enhancer/solubilizer. Clearly, Beier et al. et al's inventive transdermal system encompasses version without the permeation enhancers. .

With regards to the limitation in the new claim 19, of no additional pressure-sensitive adhesive top plaster for fixing to the skin, Beier et al.'s inventive matrix patch does not comprise of an additional pressure sensitive adhesive top plaster for fixing to the skin as detailed below. Durif et al. recited in the rejection below also teaches transdermal dosage forms comprising multilayered discoid patch which comprises an occlusive backing layer attached to the adhesive matrix in which a permeation enhancer and Apo morphine are dispensed in varying concentrations. Durif et al. does not teach the presence of a pressure sensitive adhesive top plaster for fixing to the skin in his formulation. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to develop a transdermal therapeutic system comprising pramipexol with in a two active –ingredient containing polymer layer comprising different concentrations of active ingredient and a pressure sensitive adhesive polymer in the absence of a permeation enhancer and with no additional pressure sensitive adhesive top plaster for fixing to the skin.

Original rejection:

Beier et al. teaches an active-ingredient containing matrix-controlled transdermal therapeutic system (TTS) for the use of pramipexole, ropinirole, pharmaceutically acceptable salts thereof or pharmaceutically acceptable derivative thereof (abstract).

Beier et al.teaches a transdermal therapeutic system for the administration of pramipexole comprising an (i) an active ingredient-impermeable cover layer (ii) a plurality of active ingredient containing matrix layer (iii) a peel-off protective layer. Beier et al. teaches that a matrix-TTS comprising pramipexole and ropinirole as active ingredient is to a large extent stable towards decomposition if a self adhesive matrix based on polyacrylates, especially solvent-containing polyacrylates or an polyisobutylene is used [0015]. A matrix-TTS according to **Beier et al. consists of an impermeable cover layer, one or more self-adhesive matrix layer(s) containing the active-ingredient and where applicable permeation enhancers/solubilize**r, or one or more matrix layer(s) that are coated with a pressure-sensitive adhesive, and a peel off protective layer and the active ingredient contained in the matrix is pramipexole, ropinirole its salts or derivatives [0016]. The amount of pramipexole, ropinirole, salts or derivatives used in the transdermal therapeutic system of Beier et al. ranges from 2-15% by weight of the matrix [0018]. Beier et al. teaches that active ingredient to be pramipexole, ropinirole or pharmaceutically acceptable salts of pramipexole or derivatives, solvates with the active ingredients such as hydrates and alchoholates [0017] Beier et al. teaches that for pressure-sensitive adhesive layer, a pressure-sensitive adhesive based polymer such as polyurethane, polyisobutylene, polyvinylether, silicone, polyacrylate or a mixture thereof can be selected [0020] For the matrix, matrix formers customary in medicine are used e.g. polyacrylates and polyisobutylene and the matrix formers based on polyacrylates may be any desired homopolymers, copolymer or tetrapolymer consisting of various acrylic acid derivative,

where applicable with vinyl acetate [0021-0022]. Beier et al. teaches various monomers to be used in his invention which includes esters of acrylic and methacyrlic acids such as butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, etc that may be polymerized individually or in admixture [0024]. In addition functional monomers that are compolymerisable with the acrylates and methacyrlates include hydroxyethyl acrylate, hydroxypropyl acrylate can be used too [0025], Further more Beier et al. teaches examples wherein the composition of a self-adhesive matrix transdermal therapeutic system for pramipexole includes pramipexole, Copherol and Durotak 2287 [0030] and [0048]. *Durotak 2287 is the polymer recommended by the applicant in the instant specification and used in the instant examples (page 7, line 34 to page 8. line 5, example 1 and 2 on page 12 of instant application).*

The teachings of Beier et al. differs form the instant application in that although Brier teaches multiple layer, he fails to teach the transdermal therapeutic system specifically including a second active ingredient containing polymer layer comprising between 2-10% pramipexole as recited in claim 1. Beier et al. is also silent as to the Pramipexole being in the form of and S (-) enantiomer, the flux rate greater than 5 $\mu g/cm^2$ hr or a delivery rate of pramipexole of 0.5-4.5 mg/ day. These deficiencies are taught by Durif et al. and Hoffman et al further in view of Zierenberg et al. and Patel.

Durif et al. teaches dosage forms for the transdermal administration of apomorphine (abstract). Durif et al. teaches that apomorphine is a powerful and effective agent for treatment of Parkinson's disease abnormalities (col.1, lines 45-60 and col.12, lines 58-64). Durif et al. teaches an embodiment wherein the dosage form is

a multilayered discoid patch in which the concentration of apomorphine and permeation enhancer in the adhesive matrix varies in adjacent layers (col.8, lines 22-25). Durif et al. et al teaches dosage form that has a skin contact adhesive layer containing a relatively high concentration of a permeability enhancer such as BHT and a relatively low concentration of apomorphine. Successive additional adhesive layers are placed upon the preceding layer, where each successive layer has a relatively lower concentration of permeation enhancer and a relatively higher concentration of apomorphine present and an occlusive backing layer is present as the top layer of the dosage form (col.8, lines 34-47). One embodiment of the dosage form of the present invention is a transdermal patch that contains an occlusive backing layer attached to the adhesive matrix on a face opposed to the surface capable of adhesively contacting a skin surface, and a release liner attached to the skin contact surface of the adhesive matrix. The adhesive matrix in this particular embodiment contains the pressure-sensitive medical-grade silicon adhesive, a permeation enhancer and apomorphine and may can contain a plurality of layers where each successive layer contains in addition to the adhesive varying concentrations of apomorphine and/or a permeation enhancer (col.12, lines 35-51). As such Durif et al. et al provides an ordinarily skilled artisan ample motivation to develop a transdermal therapeutic system comprising two different layers, each containing the adhesive matrix with varying concentration of active ingredient.

Hoffmann et al.teaches a transdermal patch for drug delivery of such therapeutic agents as antimigraine agents, comprising a protective impermeable backing layer, a reservoir layer, an adhesive layer, and a removable cover layer (column 2, lines 4-21 and 47-68;

column 3, lines 4-6; claim 1). The backing layer is the outermost layer of the patch, the reservoir layer is adjacent to, and in contact with, the backing layer and contains the drug or drugs at a high concentration (supersaturated), the adhesive layer is positioned immediately after the reservoir layer and can contain the active agent in a concentration lower than in the reservoir layer, and the removable covering is attached to the adhesive layer (column 2, lines 48-68; column 3, lines 1-6; Figure 1). The reservoir layer further comprises a polymer matrix, such as polyisobutylene and other polymers which have been used in the production of pressure sensitive adhesive materials may be used, and can also comprise carrier agents for the therapeutic agent, and/or a filler (column 3, lines 47-66; column 4, lines 1-6; Example 1). Hoffmann et al. additionally teaches that the transdermal therapeutic system of his invention can be used to other therapeutically active agents which are administered to the skin (col.4, lines 17-23). The adhesion layer further comprises a polymer matrix, such as polyisobutylene, and can also comprise carrier agents for the therapeutic agent, and/or filler (column 4, lines 38-51; column 3, lines 47-66; column 4, lines 1-6; Example 1). Although Hoffmann et al. does not teach specific amounts of the components of the compositions, Hoffmann et al. does teach that the desired release rate of the active agent can be controlled by adjusting the composition of the polymer matrices, the concentration of the active agent in the reservoir and adhesive layers, the concentration gradient, and the kind and amount of carrier agents (column 5, lines 13-32). Hoffmann et al. also teaches some embodiments in which the reservoir layer is made up of multiple layers with different concentrations of active agent (concentration increases as distance from skin increases,

or as the layers get closer to the backing layer). Hoffman further teaches that the various individual layers of the reservoir layer may be produced from either the same or different polymer matrix and the therapeutically desired amount is determined by the kind of the active agent or agents, the intended time of the application of the medical bandage and the intended therapeutic field or therapeutically indication for the pharmaceutical product. Hoffman et al additionally teaches that the ratio of drug concentration in g per cm3 in the individual layer of the supersaturated reservoir layer adjacent to the adhesive layer to the drug concentration in the individual layer of the supersaturated reservoir layer closest to the cover layer is within the range of 1:1.1 to 1:20, preferably 1:2 to 1:20.

Neither Durif et al. nor Hoffman et al. teaches the instantly Pramipexole being in the form of and S (-) enantiomer, finally the flux rate greater than 5 $\mu g/cm^2$ hr or a delivery rate of pramipexole of 0.5-4.5 mg/ day.

However, Zierenberg et al. teaches transdermal administration of 2-amino-6-n-propylamino-4, 5, 6, 7-tetrahydrobenzothiazole (Pramipexole) or the (-) enantiomer thereof and transdermal systems containing these active substances (abstract). Zierenberg et al. teaches that transdermal administration of Pramipexole, doses of 2 mg per day can be administered without an orthostatic side effects occurring in the patient, which corresponds to 10 times the amount which can usually be administered by oral application of the substance (col.1, lines 30-38). Zierenberg et al. additionally teaches that although the solution to his invention is not limited to the use of a specific transdermal therapeutic system, provided the system ensures an adequate release of

active substance-systems which have an active substance reservoir consisting of an emulsion polymerized polyacrylate are preferred according to his invention. Using such systems Zierenberg et al. teaches that it is possible to administer 2-amino-6-n-propylamino-4, 5, 6, 7-tetrahydrobenzothaizole or the (-) enantiomer thereof in a dose of 0.5-5 mg per day without any orthostatic side effects being observed (col.1, line 49 to col.2, line10, claim 9). Zierenberg et al. additionally teaches that his system consists of a backing layer which is impervious to the active substance and is simultaneously as a covering plaster to secure the system to the skin, a reservoir containing the active substance and a removable protective film which protects the system before it is ready to be used and the preferred carrier material polyacrylate is the type marketed as Eudragit NE (a mixture of carboxyl-group-free polymerized acrylic esters and methacrylic esters). The proportion of the active substance in the reservoir is between 5-30% preferably between 7-15% by weight (col.2, line 11-23).

Patel et al. teaches transdermal formulations comprising ropinirole for use in treating Parkinson's disease (abstract). Patel teaches that the transdermal formulation offers the advantage of a more convenient mode of administration of the drug substance, thereby potentially enhancing patient compliance and in addition, drug substance is released in a more controlled fashion, over a prolonged period, offering potential therapeutic advantages (page 1, lines 29-32). Patel teaches that the transdermal system of his invention will provide a steady rate delivery, or alternatively a compartmentalized rate controlled system and a suitable target skin flux will be in the range of 5-25 preferably in the range of 10-15 ug/cm^2/hr (page 3, lines 10-13 and page

7, claims 2). Patel teaches the transdermal formulation to be provided in a unit dose form, in a range of dosage amounts, for instance to allow for titration of an individual patient's drug requirement and a suitable dose may be obtained by combining different strength formulation. Patel teaches a unit dose form to provide sufficient drug substance for a 24 hour period to permit once-a-day application of the formula (page 3, lines 21-28). Patel also teaches the penetration of drug from the transdermal system of his invention over 254 hours and 96 hours in Example 3 (page 5-6) where in ropinirole free base displays a penetration of about 10-20 ug/cm^2 over 24 hours and 30-84 ug/cm^2 of the drug had penetrated over a period of 96 hours. Both Pramipexole and Ropinirole are non-ergoline dopamine agonists commonly used in the treatment of Parkinson's disease as evidenced by D.J Brooks (J. Neurol.Neurosurg. Psychiatry, 2000; 68; 685-689) who teaches on page 687, under the heading Non-ergoline Agonists that ropinirole and pramipexole are both new dopamine both of which act as agonists of D2-type receptors. Therefore, Pramipexole and Ropinirole are functional equivalents. Additionally, Beier et al. et al, teaches the use of these two drugs together in a transdermal system providing a suggestion that one of ordinary skill in the art could use pramipexole in place of Ropinirole in the transdermal system taught by Patel.

With regards to the limitation in instant claims 1, 14 and 18 of the concentration by weight of the pramipexole in the first and the second active-ingredient layer, Beier et al. teaches his transdermal therapeutic system to comprise pramipexole or ropinirole at a concentration of 2-15% by weight of the matrix. Beier et al. as such provides an ordinary skilled artisan a starting concentration to optimize the active ingredient.

Additionally, Hoffmann et al. teach that the desired release rate of the active agent can be controlled by adjusting the composition of the polymer matrices, the concentration of the active agent in the reservoir and adhesive layers, the concentration gradient, and the kind and amount of carrier agents. Hoffman additionally teaches the ratio of the active ingredients in subsequent matrix layers which provides an ordinarily skilled artisan teaching as to optimize the concentration of the active ingredient among the different layers. As such determination of the amount of active ingredient which needs to be incorporated in the various matrix layers in a multi layer transdermal therapeutic system would have been obvious to one of ordinary skill in the art at the time of this invention. Additionally, It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

In view of the foregoing references it would have been *prima facia* obvious for one of ordinary skills to develop a therapeutic transdermal system as instantly claimed with two layers comprising active ingredient at different concentrations. Because Beier et al. teaches that a matrix-Transdermal Therapeutic System comprising pramipexole and ropinirole as active ingredient is to a large extent stable towards decomposition if a self adhesive matrix based on polyacrylates is used, Durif et al. et al and Hoffman et al teaches transdermal systems with more than one pressure sensitive adhesive layer comprising different concentrations of the active ingredient, Zierenberg et al. teaches the reduction of orthostatic side effects in delivering pramipexole as transdermal

therapeutic form and Patel teaches that transdermal forms offers several advantages over oral administration such as patient compliance and controlled delivery of the drug. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to develop a transdermal therapeutic system comprising pramipexole with in a two active –ingredient containing polymer layer comprising different concentrations of active ingredient and a pressure sensitive adhesive polymer. An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success based on the state of the art at the time of invention that such a transdermal therapeutic system would be an effective system for delivery of pramipexole as it offers longer duration of constant delivery and higher stability.

With regards to limitations claimed in instant claim 11 wherein the drug is delivered continuously to a patients' skin over a period from 4 to 7 days, and limitations in the instant claims 1 and 12 of the active ingredient being released over a period between 24 hours after administration to 72 hours or 168 hours, designing transdermal therapeutic systems for delivery of drugs continuously for desired time period at the rate is well known in the art as evidenced by Scheindlin (Molecular Interventions 4: 308-312 (2004)) who teaches on page 308, the scopolamine patch is worn behind the ear and releases the alkaloid for three days, preventing motion sickness without the need to swallow tablets periodically, the fentanyl patch acts for seventy-two hours, providing long lasting pain relief and an estrogen-progestin contraceptive patch which has to applied once a week. Accordingly, one of ordinary skill in the art would be able to formulate the transdermal therapeutic system for pramipexole as taught by Beier et al.,

Zierenberg et al. and Patel to have the desired release profile ranging from once a day to once a week administration.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Claims under 35 U.S.C. 103(a) as being unpatentable over Beier et al.(WO 03/015779 as translated by US 2004/0247656) in view of Durif et al. et al, Zierenberg et al. et al, (US 5112842) and Patel et al (WO 96/39136) as applied to claims 1-3, 6-12 14-15 and 17-18 above further in view of Wick et al (US 5238944, already of record)

Teachings of Beier et al., Durif et al., Hoffmann et al., Zierenberg et al. and Patel are as discussed supra and are applied here in the same manner.

Durif et al. additionally teaches his inventive transdermal system to comprising a pressure-sensitive medical grade silicone adhesive mixture which contains apomorphine and a penetration enhancer (col.3, lines 39-44, and col.9, lines 31-41). Durif et al. additionally teaches the method of preparation of the silicone pressure sensitive composition which does not comprise water or an aqueous dispersion (col.9, lines 42-col.11, line 66).

The cited references do not teach the pressure sensitive adhesive monomer mixture comprising vinyl acetate in a proportion of between than 25% by weight.

Wick et al. teaches pharmaceutical formulations and adhesive-coated sheet materials for transdermal delivery (abstract). In one of the embodiment of the pressure sensitive adhesive composition, Wick et al teaches the adhesive copolymer to comprise about 60-80% by weight of the hydrophobic monomeric acrylic or methacyrlic acid ester

of an alkyl alcohol, 4-9% of reinforcing monomer selected from the group consisting of acrylic acid, methacrylic acid etc. and about 15-35% by weight of vinyl acetate based on the total weight of all monomer in the copolymer.

As such, use of pressure sensitive adhesives as taught by the above references was well known in the pharmaceutical art at the time of the invention. Pressure sensitive adhesive compositions comprising co-polymers of monomeric acrylic or methacrylic acid with vinyl acetate was also known in the art at the time of the invention. Accordingly, it would have been obvious to one skilled in the pharmaceutical art to optimize the known polymers suitable for preparing pressure sensitive adhesives and its concentration to arrive at a composition of pressure sensitive adhesive layer which would provide good adhesion to the skin and optimal delivery of the drug through the skin. As such an ordinarily skilled artisan would apply the knowledge of developing an appropriate pressure sensitive adhesive as taught by Durif et al. and Wick to be used in the pramipexole transdermal delivery system taught by Beier et al., Durif et al., Hoffman Zierenberg et al. and Patel with a reasonable expectation of success.

(10) Response to Argument

A. Response to Appellant's argument against the new matter rejection of Claim 1 and dependent claims 2-3, 6-12, 14-17 and 19-20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Appellant's argue against this rejection as follows: Their disclosure recites an exemplary construction of Example 2, "consists of, "i.e. is limited to a total of three layers, a backing layer, a reservoir layer and a pressure-sensitive adhesive layer" and as such one skilled in the art would clearly understand that the backing layer and the pressure sensitive adhesive layers constitutes the two outermost layers of the TTS and the reservoir layer disposed between the two layers and consequently, as the "closed phrase" "consisting of" language describing Example2, the first active layer must be directly disposed upon both the outer layers, hence it is directly disposed upon the backing layer.

While the Appellant's arguments are considered, they are not found to be persuasive. Examiner would like to note that "directly "is understood to mean with "contact" or "without anything intervening" or "touching each other". Appellant's reference in their specification as stated in their argument does not disclose this kind of contact between the active ingredient-containing polymer layer and the backing layer and as such the phrase "disposed directly on the backing layer" in claim 1 constitute new matter and the claim is therefore appropriately rejected in this rejection.

B. Response to Appellant's argument against rejection of claims 1-3, 6-12 14-16 and 17-20 under 35 U.S.C. 103(a) as being unpatentable over Beier et al. et al, Durif et al., Hoffman et al., Zierenberg et al. et al, Patel et al and Wick et al.

Appellants traverse this rejection with the following arguments:

a. Beier et al. merely discloses that moderate amounts of pramipexol may be incorporated into polymers and the prior art reference teaches that elevated concentrations of active ingredients, such as a 10% loading, within polymer matrices cause a loss of adhesion, thus requiring an additional adhesive layer adjacent to the backing layer. Examiner has indulged in impermissible hindsight analysis by picking and choosing elements from the prior art while using the instant application as a guide. With regards to instant claim 18, Beier et al. teaches the incorporation of penetration enhancers for Pramipexol in the acrylic matrices, while Zierenberg et al. teaches the use of a top plaster in combination with Pramipexol formulations. Durif et al., Hoffmann et al. and Patel are not directed to pramipexole.

b. Beier et al. is directed to TTS's providing improved shelf stability that include a maximum of 15% by weight of active ingredient, Beier et al. teaches acrylic acid and methacrylic acid a suitable monomer within its matrix polymer, Beier et al. merely notes that its system may include one or more matrix layer and that permeation enhancers may be included "where applicable" . Working examples of Beier et al. incorporate permeation enhancer in conjunction with acrylic-based matrix layers and teaches the incorporation of 2.5-3% weight % active ingredient within a single layer-based matrix

and Zierenberg et al. teaches TTS's which included covering plaster and the examples of Zierenberg et al. include 9 wt% active substances in a single layer.

c. Durif et al. is directed to apomorphine delivered in a discoid dosage form containing permeation enhancer where in the apomorphine is at a concentration of 10% by weight and both apomorphine and penetration enhancer "differ in amount in each layer".

d. Hoffmann et al. does not teach a suitable range of amounts of active agent with its reservoir layers but expressly note that elevated quantities of active ingredients may cause the layer to lose its adhesive power and thus require an additional adhesive intermediary layer, the working examples of Hoffmann et al. contain about 10% active ingredient.

e. Patel is directed to the use of ropinirole and teaches a single drug-containing layer with the TTS and the matrix is made up of polyvinyl alcohol and polyvinylpyrrolidone and penetration enhancers may be added, One would not transfer the teachings from other active ingredients e.g. apomorphine of Durif et al., as these active ingredients have a significantly different chemical constitution and associated physical properties.

f. Wick et al. is directed to formulations for the topical or transdermal delivery of an anti-viral and is directed towards a single layered transdermal devices and Wick further indicates that skin penetration enhancers may be incorporated.

Appellant's traversal arguments have been fully and carefully considered, but fail to be persuasive,

First, In response to applicant's arguments against each references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For example. In the instant case, (i) although Beier et al. dose not specifically teach the pramipexole being in the S (-) enantiomer form, Zierenberg et al. teaches this limitation. (ii) Although Beier et al. does not teach the flux rate of the active ingredient release, this limitation is taught by Patel et al. (iii) Although Beier et al. only teaches a moderate amount of pramipexol in their system as alleged by the applicant, Hoffman teaches that the desired release rate of the active agent can be controlled with the concentration of the active ingredients in the subsequent matrix layers which provides an ordinarily skilled artisan motivation to optimize the amount of active ingredient which needs to be incorporated in the various matrix layers in a multi layer transdermal system. (iv) Beier et al. while suggesting a plurality of active ingredient containing matrix layer is further supported by the teachings of Durif et al. and Hoffman et al who teaches more of such systems and further provides an ordinarily skilled artisan suggestions as to the method of preparing such systems and their advantages. As such In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to

one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). All the references here are drawn towards the same art which is transdermal delivery of therapeutic substances. Accordingly, an ordinarily skilled artisan in the pharmaceutical arts at the time of the invention would be motivated to combine the teachings of these references to arrive at the instant invention.

Secondly, In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In this regard, the cited prior art teaches TTS systems comprising one or more layers which are composed of active ingredients such as pramipexole in a self adhesive matrix based on polyacrylates comprising different concentration of the active ingredient. Design and use of Transdermal therapeutic systems (TTS) and the advantages of delivering Pramipexole in the TTS form was well established and routine in the art at the time of the instant invention. As such, there is nothing unobvious about taking combining the teachings of Bier with the teachings of Zierenberg et al., Durif et al., Patel and Hoffman et al. and arriving at the instantly claimed system. Applicant's disclosure is not needed to provide any motivation in this regard because the

transdermal art in pharmaceutics is well developed and the teachings of the above references teach one of ordinarily skilled artisan method to formulate a transdermal therapeutic as instantly claimed.

Thirdly, in response to Appellant's arguments that the working examples in each of the references used in the rejection does not suggest the instant invention, such as the working examples of Beier et al. incorporate permeation enhancer and teach incorporation of 2.5-3% active ingredient within a single layer of acrylic-based matrix' the working examples of Zierenberg et al. include 9% active substance within a single layer; and the working examples of Hoffman are directed to nitroglycerine bandages and contain about 10% active ingredient " it is noted that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). . It is noted that a reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Furthermore, "[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." In re Fulton, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). As such, an ordinarily skilled artisan would be motivated from everything disclosed in the above references and not just the examples. Similarly, With regards to applicant's argument that Beier et al. merely teaches that the system may include one

or more layers and notes that permeation enhancers may be included "where applicable" , it would have been obvious to an ordinarily skilled artisan from Beier et al. teaching that his system may include one or more layer of matrix and that the permeation enhancer may be included "where applicable" when taken in combination of the other references in the rejection clearly provides motivation to an ordinarily skilled artisan to develop multi layered transdermal therapeutic systems with or without permeation enhancers.

Fourth, in response to Appellant's arguments against Durif et al., Patel and Hoffman et al that they are directed to an active ingredient having an altogether different chemical constitution for the recited pramipexol and that One would not transfer the teachings from other active ingredients e.g. apomorphine of Durif et al., as these active ingredients have a significantly different chemical constitution and associated physical properties.. The art of transdermal therapeutic systems is general and applicable to several different drugs which are administered by topical means as evidenced by Hoffman et al. who teaches that the transdermal therapeutic system can be applied to many therapeutically active agents which are administered to the skin with or without resorption improving agents and which produce local or systemic effect and includes fungicides, bactericides, bactriostatics, antibiotics, hormones, antipyretics, antidiabetics, analgetics, etc. Nowhere in their documents that Durif et al. et al or Patel disclose that their transdermal system is specific to the active ingredient they are teaching. It is also noted that Durif et al. or Patel or Hoffman et al. does not recite anywhere that their inventive TTS is not conducive to use with other therapeutic agent. It is also noted that

ropinirole An ordinarily skilled artisan would be motivated to utilize the multilayered transdermal therapeutic system taught by Durif et al. each layer having different amounts of the therapeutic system in developing TTS for other active agents especially those which are already know to be more useful when delivered transdermally such as venlafaxine. Appellants have not provided any evidence to their allegation that the active agents with significantly different chemical constitution and associated physical properties requires specific properties in transdermal systems for efficient delivery each of which is distinct from the other.

Fifth, With regards to Appellants argument against Hoffman et al., that Hoffman et al. does not teach a suitable range of amounts of active agents with its reservoir layers, but notes that elevated quantities of active ingredients may cause the layer to lose its adhesive power, thus requiring an additional adhesive intermediary layer, It is noted first that Hoffman et al. teaches that "the increase of the active agent **may** cause a decrease in the adhesive power" and in addition does not provide the exact concentration which decreases the adhesive power. Further, Hoffman et al. teaches the adhesive layer if needed may be produced from the same material as the polymer matrix without the resorption improving agents and carrier materials and teaches that this layer may also comprise of active agent at saturation concentration. (Hoffman et al., col.4, lines 27-51). As such the adhesive layer suggested by Hoffman et al. would have the same polymer matrix but different amount of active agents and is therefore suggestive of the instantly claimed system.

Sixth, with regards to Appellants argument against Wick et al., Examiner would

like to point to the fact that Wick et al. is also drawn to the same art of transdermal delivery system and is included in the rejection for their teachings of use of vinyl acetate as pressure sensitive adhesive. Use of pressure sensitive compositions in transdermal therapeutic systems was well known in the art at the time of the instant invention. The pressure sensitive adhesive with vinyl acetate was also known to be useful for the same purpose as taught by Wick et al. and as such it would have been obvious to an ordinarily skilled artisan to utilize the pressure sensitive adhesive taught by Wick et al instead of the others in the development of a transdermal system simply based on the fact that they are functional equivalents.

Finally, Appellant opines that Beier et al. et al. alone or Durif et al. et al. alone or Hoffman et al alone or Zierenberg et al. et al alone or Patel alone or Wick et al. alone does not disclose each feature of the claim. This is unpersuasive. The finding of obviousness was based upon the teachings of Beier et al. taken together with the teachings of the other references. The instant rejection is predicated on the finding that one of skill in the art would have been motivated to combine the elements as taught by Beier et al. (i.e., a transdermal therapeutic system for administration of pramipexol comprising an active ingredient impermeable cover layer, a plurality of active ingredient containing matrix layer which may not include a permeation enhancer) with Durif et al. and Hoffman et al.. (i.e., teachings of transdermal systems with more than one pressure sensitive adhesive layer comprising different concentrations of active ingredient), Zierenberg et al. (i.e., reduction of orthostatic side effects in delivering pramipexole as transdermal therapeutic form) and Patel (i.e. the several advantages offered by

transdermal administration). in order to arrive at the transdermal therapeutic systems as instantly claimed. In other words, the prior art at the time of the invention clearly suggested and motivated a transdermal therapeutic system with multiple layers each layer comprising varying amounts of active ingredient (high and low) with a backing layer where in the active ingredient is dispersed in a polymer matrix.

In making such a combination, the skilled artisan would have necessarily considered the prior art generally available at the time of the invention regarding the claimed elements, uses of the claimed elements and reasons or suggestions to combine such elements.

In view of these facts, Appellant's argument that the prior art does not suggest such a Transdermal therapeutic system is unpersuasive. The cited prior art provides a clear teaching, suggestion and motivation to combine the elements of Beier et al., Durif et al., Hoffman et al, Patel and Zierenberg et al. to develop a transdermal therapeutic system, in fact, the same as that of the instant claims.

For these reasons set forth *supra*, and those previously made of record at p.2-22 of the previous Office Action dated July 6th 2010, rejection of claims **1-3, 6-12 and 16-20** remains proper.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/SAVITHA RAO/

Examiner, Art Unit 1614

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/Ardin Marschel/

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